REMARKS

Applicants now respond to the non-final Office Action of August 25, 2004. Claims 1, 2, 7-19 and 21-28 are pending in this application. The Office has rejected claims 1, 2, 7-19 and 21-28 under 35 U.S.C. §§ 112 and 102. The Applicants respectfully traverse and request withdrawal of these rejections in light of the comments now presented in this response.

35 USC § 112

The Office has rejected claims 1-2, 7-19 and 21-28 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Stating that the complete etiology and pathogenesis of Alzheimer's disease is unknown, the Office concludes that primary prevention is infeasible and thus complete prevention of Alzheimer's diseases is not enabled.[1] Applicants respectfully disagree with the Office's characterization of the claims and the resulting conclusion that the application lacks enablement.

The Applicants have not claimed "primary" or "complete" prevention and do not venture to define those terms. Rather, the independent claims simply recite "a method for the prevention of Alzheimer's disease." "Preventive" can be defined as "tending to defeat or hinder."[2] "Hinder" can be defined as "prevent from starting or moving forward, to check, retard, impede, delay, stop, interrupt, thwart." Thus, the definition implies that a method of prevention need not forestall the disease completely. Prevention may also be achieved by delaying the onset of the disease or slowing the course of the disease. As recited in the specification, other therapies, e.g., the nicotine patch, are being tested "to lessen the symptoms or delay the progression of the disease" (Specification, page 3, lines 23-24).

---

[1] Applicants assume that the Examiner made a typographical error and excluded the word "not" before "enabled" in the first line on page 3 in the pending Office Action.

[2] Definitions within this paragraph were obtained from the On-line Medical Dictionary, accessed at http:// http://cancerweb.ncl.ac.uk/cgi-bin/omd on November 30, 2004.

As disclosed in the specification on pages 2-4, a number of therapeutic agents are under investigation for treating and preventing Alzheimer's disease. The therapeutic effects of these agents are based upon different biochemical approaches. These include, for example, the use of an asparyl protease to inhibit cathespin D, the use of an hypoxanthine analog to promote nerve regeneration, the use of CX516 to promote the uptake of Ca^{2+} into nerve cells, the correlation of nicotine or estrogen with a lower incidence of Alzheimer's disease, and the use of prednisolone to reduce inflammation in the brain. Thus, when the Applicants state at page 2, lines 10-11, that "there appear to be other mechanisms involved [in the pathogenesis of Alzheimer's disease]," they are not discounting what is known regarding amyloid plaque deposition and how that knowledge has led to the instantly claimed method to prevent Alzheimer's disease. Rather, the Applicants acknowledge that, theoretically, other known and unknown mechanisms may also be involved in the pathogenesis of Alzheimer's disease.

The Applicants are claiming a method of prevention, not all methods of prevention, nor "complete" or "primary" prevention, whatever those terms may imply. The instantly claimed method of prevention is based upon the observation of over-expression of neural tread protein ("NTP") in Alzheimer's disease neurons (Specification, page 2, lines 23-25) and that high levels of circulating insulin relates to increased expression of NTP in nerve cell culture (Specification, page 4, lines 18-21). [3]

[3] On page 4, lines 18-19, Applicants state that "[t]he present invention is related to the discovery that high levels of circulating insulin are a root cause of Alzheimer's disease." This statement should not be interpreted to mean that Applicants have tested insulin levels in patients with Alzheimer's disease or correlated high levels of circulating insulin to the induction of Alzheimer's disease. See Example 1 for results of Applicants testing in support of this quoted statement.

The standard for determining whether the specification meets the enablement requirement is "whether any person skilled in the art can make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). Whether any necessary experimentation is undue is typically analyzed by the factors listed in *In re Wands at 737*, which include but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) That state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Before this can be done, the Office must construe the claims, and for those terms that could have more than one meaning, the examiner must select the definition that she intends to use when examining the application. *Genentech v. Wellcome Foundation*, 29 F.3d 1555, 1563-64 (Fed. Cir. 1994). The Office is then obligated to analyze all the evidence related to each of the Wands factors in reaching a conclusion regarding enablement.

Here, as described above, the Office has incorrectly construed the meaning of "prevention" and has failed in its analysis to establish a *prima facie* case of nonenablement. The Office acknowledges that the level of skill in the art is high but has not addressed the guidance provided by the inventors. The inventors begin by describing the relationship of amyloid β

peptide to the amyloid plaques, the centers for the degeneration of nerve endings, that are deposited around and between the nerve cells in the brains of those with Alzheimer's disease (Specification at page 2, lines 3-6). The inventors go on to described an epidemiological correlation between the deposition of amyloid in islet cells, leading to glucose intolerance and non-insulin-dependent diabetes mellitus, and amyloid β-protein deposition in brain cells as associated with Alzheimer's disease (*Id.* at lines 17-22). The inventors also disclose that there is evidence of the over-expression of a protein called neural tread protein (NTP) in Alzheimer's disease neurons and that this protein has been cloned and expressed in cell-free culture.

They base the instantly claimed methods upon the discovery that insulin stimulates the increased expression of NTP in nerve cell culture (*Id.* at page 4, lines 18-23). It follows that the administration of an agent to lower serum insulin levels, such as one that is also useful for treating impaired glucose tolerance, would treat or prevent Alzheimer's disease. A number of therapeutic approaches to controlling insulin levels are described at pages 5-8 in the specification. The agents claimed here are chromium and certain thiazolidinediones. A dietary approach of restricting metabolizable carbohydrates is also described.

The inventors explain that the insulin receptor requires chromium to function properly and that a deficiency in chromium is rampant in the American diet (*Id.* at page 6, lines 4-8). Thus, supplementing the diet with chromium has been shown in animals to lower serum insulin levels. The inventors also describe the thiazolidinediones and related antihyperglycemic agents as useful for treating impaired glucose tolerance in order to prevent or delay the onset of non-insulin-dependent diabetes mellitus. The specification cites U.S. Patent Nos. 5,478,852 and 5,457,109 as further evidence of the specific structure of these compounds and their therapeutic properties.

Finally, the inventors describe why a dietary approach to decreasing insulin levels would treat or prevent Alzheimer's disease (*Id.* at page 8, lines 8-22). The restriction of metabolizable carbohydrates in the diet has been designed to reduce serum insulin levels to normal levels, and thereby treat other symptoms of insulin insensitivity. By correlating insulin insensitivity with higher levels of serum insulin it follows that restricting metabolizable carbohydrates would also help to treat or prevent Alzheimer's disease (*Id.* at page 5, lines 13-24).

In addressing the working examples, the Office states the specification only exemplifies a test for regulating insulin signal transduction cascade that subsequently influences NTP gene expression and fails to show any human or animal involvement.[4] Example 1 in the specification (pages 10-11) provides an expanded biochemical explanation of the relationship between insulin, CNS neurons, and increased levels of NTP. Working examples, however, are not required for enablement. "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 27 U.S.Q.2d 1510, 1513 (Fed. Cir. 1999). The "absence of a working example, denominated as such, does not compel the conclusion that a specification does not satisfy the requirements of 35 U.S.C. 112." *In re Long*, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966).

The Office also states that there was no complete prevention or cure for Alzheimer's disease as evidenced by numerous documents available at the time of the invention and lists four references on PTO-892. Applicants respectfully remind the Office that they are not claiming "complete prevention or a cure." Also, of the documents listed, Gottfires and Mandelkow were published in 1994, approximately four years before March 12, 1998, the filing date of the PCT to

[4] Applicants request clarification regarding the meaning of the Office's statement beginning at the last line on page 4 of the Office Action, "Furthermore, the exemplified test does not show complete inhibition or prevention nor fat, see figure 1."

which this application claims priority, and therefore are not good indications of the state of the art, which was evolving rapidly at that time. Thomas does not address the relationship of high levels of circulating insulin to NTP expression. Rather, Thomas describes the use of non-steroidal and anti-inflammatory drugs in decreasing the risk of Alzheimer's disease by "unknown mechanisms," relating to amyloid-β aggregation, not NTP expression. Compton describes the use of hormone replacement therapy and its effect of reducing the risk of Alzheimer's disease compared to post-menopausal women who do not take hormone replacement therapy. When Compton states the neurobiological basis of these differences was unknown, he is speaking in relation to hormone replacement therapy, not the relationship of high levels of circulating insulin to NTP. None of the references listed by the Office are both timely and on point.

More recent evidence supports the enablement of Applicants' claimed invention. Applicants respectfully direct the attention of the Examiner to Combs, C.K. *et al.*, "Inflammatory Mechanisms in Alzheimer's Disease: Inhibition of β-Amyloid-Stimulated Proinflammatory Responses and Neurotoxicity by PPARγ Agonists," *J. Neurosci. 20:*558-587 (2000), cited by Applicants in the Information Disclosure Statement filed on December 18, 2003, who report that thiazolidinediones are PPARγ agonists and that they inhibit the β-amyloid stimulated inflammation responsible for neurotoxicity and astrocyte activation in Alzheimer's disease. Combs also reports that the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease is due to their actions on the PPARγ receptor rather than on cyclooxygenases. Combs, Abstract. Applicants note that troglitazone, pioglitazone, 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]-thiazolidine-2,4-dione and englitazone, all recited in claim 1, are thiazolidinediones, and thus are PPARγ receptor agonists

Combs also recount studies showing that patient populations treated for extended periods with NSAIDs exhibited a dramatic reduction in the risk of Alzheimer's disease. Combs at page 558, second col., lines 20-23. Clearly, in those patients who received these PPARγ receptor agonists and did not develop Alzheimer's disease, the disease was prevented.

Finally, Applicants respectfully direct the attention of the Examiner to Wilson, T.M. *et al.*, "The PPARs: From Orphan Receptors to Drug Discovery," *J. Med. Chem. 43:*527-550 (2000), cited by Applicants in the Information Disclosure Statement filed December 18, 2003, who report that the thiazolidinedione rosiglitazone was identified as a high affinity subtype-selective agonist for PPARγ and that the rank order of PPARγ potency of a number of thiazolidinediones closely match their glucose-lowering activity in rodents. Wilson *et al.* conclude that there is compelling evidence that PPARγ is the major receptor mediating the antidiabetic activity of thiazolidinediones. Wilson *et al.*, at page 532, col. 1, lines 25-32

Taken together, Combs *et al.* and Wilson *et al.* provide convincing evidence that thiazolidinediones such as troglitazone, pioglitazone, 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]-thiazolidine-2,4-dione and englitazone, all recited in claim 1, are PPARγ agonists and that such agonists are expected to be useful for preventing Alzheimer's disease.

For the foregoing reasons, Applicants contend that claims 1-2, 7-19 and 21-18 are enabled under 35 U.S.C. § 112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the lack of enablement rejections.

35 USC § 102

The Office has rejected claims 1, 2, 7-19 and 21-28 under 35 U.S.C. § 102(b) as being anticipated by the instant application and the references cited therein. The Office states that by

disclosing the use of the claimed compounds (e.g. thiazolidinediones, chromium) or restricting metabolized carbohydrate in various treatments (e.g. diabetic mellitus), and by teaching the administration of said compounds to the subject in overlapping dosage amounts, they inherently possess protective utility. Applicants respectfully disagree. The instant claims are patentable as a new use for a known composition based on unknown and unobvious properties of the composition. In addition, the Office has not been met its burden in establishing inherency.

A prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently, to anticipate. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). To assert a rejection based on inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Here, the Office describes anticipation by the "instant application and the references cited therein (see pages 6-10)," and then lists various patents within the specification. The patents are characterized as "silent about the prophylactic use of said compounds in preventing Alzheimer's disease." Further, the Office concludes that by teaching the administration of said compounds to the subject in overlapping dosage amounts, the references "inherently posses such protective utility as the claimed invention." A rejection based upon such broad, sweeping, nonspecific conclusions is clearly improper. The Applicants are entitled to know exactly which references form the basis for the rejection and exactly which dosage amounts are being compared. For this reason alone, the rejection must be withdrawn.

Assuming, *arguendo*, that the Office did provide sufficient detail, the rejection remains improper. The MPEP offers the following guidance (MPEP § 2112). The discovery of a new use for a known structure based on unknown properties of the structure might be patentable to

the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248 (CCPA 1978). Here, the use of, for example, a thiazolidinediones in the prevention of Alzheimer's disease was not contemplated by those skilled in the art at the time the application was filed. The thiazolidinediones were considered a recent development in oral antidiabetic agents. The discovery of previously unknown properties of the thiazolidinediones, i.e. its effect in decreasing the expression of NTP in nerve cells, led Applicants to the instant invention claiming a new use for a known compound.

Similarly, preventing Alzheimer's disease with chromium, a known compound in relation to insulin sensitivity, is now based on the previously unknown property of chromium to decrease the expression of NTP in nerve cells. The restriction of metabolizable carbohydrates in the diet has been used to treat obesity, heart disease, high blood pressure, high cholesterol and triglyceride level, but not to prevent Alzheimer's disease. As in chromium and the thiazolidinediones, the ability to decrease NTP in nerve cells is an unexpected property of restricting metabolizable carbohydrates through diet.

Applicants respectfully request the Office to withdraw its § 102 rejections because the Office has not met its burden in presenting specific and adequate evidence to support a finding of inherency and because the claims are patentable as a new method of using a known structure based on previously unknown properties.

Conclusion

The Office has rejected claims 1, 2, 7-19 and 21-28 under 35 U.S.C. §§ 112 and 102. The Applicants respectfully submit that the rejections are improper and should be withdrawn based on the arguments submitted above. If the claims are not in condition for allowance, the

Applicants' representative requests that the Examiner call the undersigned at 650-849-6677. If there is any additional fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: December 21, 2004

By: _____

Lauren L. Stevens
Reg. No. 36,691
Customer No. 22,852